REMARKS

This amendment is responsive to the Office Action mailed May 19, 2004 (hereinafter the "present Office Action"). Claims 17-22, 25, 28 and 29 are under examination in the present action. All claims stand rejected. Claim 18 has been amended in the present response and new claims 49-62 have been added. Reconsideration of the present Office Action, entry of the aforementioned amendments and new claims and allowance of the application, as amended, are respectfully requested.

1. Claims 17-22, 25[1], 28 and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 5,445,832 issued to Orsolini *et al.* (hereinafter referred to as "Orsolini") in view of U.S. 5,672,659 issued to Shalaby *et al.* (hereinafter referred to as "Shalaby") and in further view of U.S. 4,383,975 issued to Fong[2] *et al.* [sic] (hereinafter referred to as "Fong"). In support thereof, the Examiner points to column 3, lines 41-43 of Orsolini as support that method described therein reads on the first step of the method of the present application since it provides for the creation of a solution. Applicant respectfully disagrees. The Examiner fails to quote lines 41-43 in their entirety, wherein Orsolini

[1] Although not specifically recited as being rejected, Applicant is proceeding on the assumption that pending claim 25 is subject to same rejections as the other pending claims since it is listed as rejected on the Office Action Summary. In addition, there is no mention in the present Office Action that claim 25 has been deemed allowable.

[2] Applicant is of the opinion that the Examiner intended to cite U.S. 4,384,975 and will proceed on that assumption.

states that "once said peptide salt is *suspended* in the organic solution of the polymeric material, this solution is incorporated into a predetermined amount of an aqueous medium." Compare that to the first step of the claimed method which involves "*dissolving* a salt of a peptide complexed with an anionically or cationically functionalized biodegradable polyester." Applicant respectfully submits that the "solution" referred to by Orsolini at column 3, lines 41-43, consisted of the peptide salt suspension in combination with the organic solution of the polymeric material and does not involve dissolving the peptide salt complex.

The method of Orsolini involves the creation of a suspension of the peptide salt alone not a solution of a dissolved peptide-polyester complex. As stated in column 1, lines 21, Orsolini stated that their method "consists firstly in converting a water-soluble peptide or peptide salt into a water-insoluble peptide salt then suspending said peptide in a solution of a biodegradable polymeric material, converting said suspension into an oil-in-water type emulsion." The summary provided by Orsolini does not teach, suggest or infer that the peptide can be dissolved. Applicant further notes that when discussing their preferred embodiments, Orsolini et al. state, in column 2, lines 12-18, that "b. said water insoluble peptide is suspended in an organic medium containing the biodegradable polymeric material in the dissolved state;

[and] c. said organic suspension is [then] dispersed… Applicants also note that Examples 1-6 of Orsolini all involve suspending the salt of a peptide (*See* Orsolini column 4, line 59) and then adding said suspension (*See* Orsolini column 4, line 60)to the solution containing the dissolved copolymer so as to obtain a suspension that was "perfectly homogeneous" (*See* Orsolini column 4, lines 64-65) and then pouring said suspension into water (*See* Orsolini column 4, line 66) containing methoxycellulose to produce an emulsion. Example 2 (*See* Orsolini column 4, line 48), Example 3 (*See* Orsolini column 5, lines 58-59), Example 4 (*See* Orsolini column 6, lines 14-16), Example 5 (*See* Orsolini column 6, line 27-28), Example 6 (*See* Orsolini column 6, line 64), Example 7 (*See* Orsolini column 7, line 3-4) and Example 8 (*See* Orsolini column 8, lines 16-17) were all made by first producing a suspension of the biologically-active peptide. Finally, Applicant directs the Examiner's attention to claim 1 of Orsolini, *See* column 13, lines 42-49, wherein the 2nd and 3rd step of the Orsolini method involve:

> (b) suspending said water-insoluble peptide salt in an organic solvent containing a dissolved biodegradable polymeric organic material to form a suspension;
>
> (c) dispersing said organic suspension in an aqueous medium to form an aqueous emulsion…

Applicant contends that the method of Orsolini requires the preparation of a suspension of the peptide salt and

not a solution thereof. Orsolini clearly distinguishes a suspension from a solution. It should be noted that when discussing the preparation of the polymer solution, Orsolini discusses "dissolving" the polymer, not suspending the polymer. *See* Orsolini column 2, line 15, column 4, line 60 and column 13, line 43. Orsolini never discusses "dissolving" the peptide salt.

The Examiner is correct that at page 16, lines 14-17 of the instant application the Applicant states that "[t]he polymer microspheres of the invention are made by either suspending or dissolving the coprecipitates, salts or complexes in a polymer solution." What the Examiner fails to appreciate, however, is that the instant application claims three processes for preparing polymer microspheres. The three process are discussed on page 3, line 9 to page 4, line 12. The first method involves neutralizing a peptide salt in an aqueous medium wherein said medium comprises a ***suspension*** of hydroxyapatite or a solution of calcium mono-hydrogen phosphate to form a precipitate. The ***second*** process which is the subject of pending claims 17-22, 25, 28 and 29 involves ***dissolving*** a salt of a peptide complexed with an anionically or cationically functionalized biodegradable polyester in an organic solvent to form a solution. Applicant contends that the pending claims do not involve the preparation of a suspension. The onus is on the Examiner to show by

extrinsic evidence how dissolving the peptide, as claimed, would produce a suspension.

Orsolini also fails to recognize the inherent benefit of decreasing the water solubility of the peptide by complexing the peptide with either mono- or multi-functional monomeric or polymeric anions or cations. In the Office Action mailed July 30, 2003, the Examiner admits that the first step of the Orsolini method "differs from the corresponding step of the claimed method in that it achieves a water-insoluble derivative of a peptide by converting it into a salt (e.g., stearate, palmitate, etc.) before adding the salt to solution [sic] of polyester in an organic solution, whereas the instant method coverts peptide into a water-insoluble complex with a polyester in the organic solution." The Examiner argues that based on a second reference, U.S. 5,672,659 issued to Shalaby *et al.* (hereinafter referred to as "Shalaby"), which teaches a method of preparing microcapsules containing biologically-active peptides and an anionically functionalized polyester[3], "one skilled in the art at the time the invention was made would be motivated to use peptide [sic] conjugates of Shalaby instead of peptide [sic] salts of Orsolini in [sic] preparing microcapsules for sustained [sic] and controlled release of peptides." The Examiner's conclusion is clearly erroneous.

[3] Applicants note that Shalaby does not discuss cationically functionalized biodegradable polyesters, only anionically functionalized polyesters.

As noted in *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993),

> when "rejecting claims under 35 U.S.C. §103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). "A *prima facie* case of obviousness is established when the teachings from the prior art itself would have suggested the claimed subject matter to a person of ordinary skill in the art." *In re Bell*, 991 F.2d 781, 782, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993)(quoting *In re Rinehart*, 531 F.2d 1048, 1051, 189 USPQ 143, 147 (CCPA 1976)). If the Examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Applicant respectfully submits that that a *prima facie* obviousness rejection of claims 17-22, 25, 28 and 29 cannot be established based on the combination of the teachings of Orsolini and Shalaby. To establish a *prima facie* obviousness rejection, it is required that the motivation come from the prior art references for the modification that results in the invention under rejection, but not from an applicant's disclosure, since obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *See*, *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-52, 5 USPQ 1434, 1438 (Fed. Cir. 1988), *cert. denied*, 109 S. Ct. 75 (1988), *on remand*, 13 USPQ2d 1192 (D.Conn. 1989). Furthermore,

"[o]bviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor." *Para-Ordinance Mfg. v. SGS Importers Int'l*, 73 F.3d 1985, 1987, 37 USPQ2d 1237, 1239 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1450, 1551, 220 USPQ 303, 311, 312-13 (Fed. Cir. 1983)). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 n.14, 23 USPQ2d 1780, 1783-84 n. 14 (Fed. Cir. 1992)(citing *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)). "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." Id. At 1266, 23 USPQ2d at 1784, (citing *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991)).

The Examiner fails to identify a sufficient suggestion to combine the secondary reference (Shalaby) with Orsolini. Rather than providing a line of reasoning to explain why combining Shalaby's teaching of anionically functionalized polymers with the process discussed in Orsolini results in the process for making polymer microspheres and nanospheres of claim 17, the Examiner merely concludes "one skilled in the art…would be

motivated to use [the] peptide conjugates of Shalaby instead of [the] peptide salts of Orsolini…"

The Examiner also readily admits that Orsolini does not teach the use of sodium oleate as a surfactant. To overcome this deficiency, the Examiner relies upon a third reference, U.S. 4,384,975 issued to Fong *et al*. The Examiner once again merely concludes that "one would be motivated to use sodium oleate as a surfactant, because Fong et al. (US 4384975) demonstrates that sodium oleate is an advantageous surfactant in preparing microparticles using oil-in-water process…" As discussed previously, such blanket conclusions without identifying in either reference a suggestion to combine the two teachings is legally incorrect. As such, the rejection of claims 17-22, 25, 28 and 29 under 35 U.S.C. §103(a) as obvious over U.S. 5,445,832 issued to Orsolini *et al*. in view of U.S. 5,672,659 issued to Shalaby *et al*. and further in view of U.S. 4,384,975 issued to Fong *et al*. is legally incorrect and should be withdrawn.

2. Claims 17-22, 28 and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Herrmann *et al*., "Biodedegradable, Somatostatin Acetate Containing Microspheres Prepared by Various Aqueous and Non-aqueous Solvent Evaporation Methods," European Journal of Pharmaceutics and Biopharmaceutics 45 (1998):75-82 (hereinafter referred to as "Herrmann") in view of U.S. 5,672,659 issued to Shalaby *et al*. (hereinafter referred

to as "Shalaby") and in further view of U.S. 4,383,975 issued to Fong[4] *et al.* [sic] (hereinafter referred to as "Fong").

Herrmann describes the preparation of somatostatin microspheres with various types of solvent evaporation methods. The Examiner states that Herrmann describes a patentably similar method to that of claims 17-22, 25, 28 and 29 involving "dissolving somatostatin salt in organic solvent, adding the solution to polylactide-co-glycolide solution in dichloromethane, forming oil-in-water emulsion, and evaporating the organic solvent."

Herrmann merely describes the oil-in-water process discussed on page 1 of the instant application. AS stated in the instant application, Applicant noted:

> Solvent evaporation is usually practiced by dissolving or suspending an active ingredient in a polymer solution, which is further dispersed in the form of droplets in a suitable medium containing surfactants capable of stabilizing the droplets, and the polymer droplets are hardened by evaporation of the solvent. When the polymer is dissolved in an organic medium and then emulsified in water, the process is called oil-in-water process (O/W). Water soluble peptides cannot be encapsulated by the O/W process, due to the partition of the water soluble peptides into the aqueous medium, resulting in low encapsulation efficiency. *See* instant application page 1, lines 16-21.

As noted by the Applicant, the main hurdle "to achieving higher encapsulation efficiency of the peptides is their water insolubility." *See* instant application page 1,

[4] Applicants are of the opinion that the Examiner intended to cite U.S. 4,384,975 and will proceed on that assumption.

lines 33-34. The Applicant reasoned that the aqueous solubility of a peptide "is considerably reduced when the peptide is present as free base, due to intermolecular interactions." *See* instant application page 2, lines 1-2. To achieve reduced peptide solubility, the Applicant formed "reversible water insoluble salts of mono-functional or multi-functional detergents and or polymers or a combination of both." *See* instant application page 2, lines 18-20. This discovery resulted in higher drug loading as well as predictable release profiles as well as encapsulation efficiency greater than 85%. *See* instant application page 3, lines 6-7.

As noted by the Examiner, the oil-in-water co-solvent method discussed in Herrmann resulted in an encapsulation efficiency of 76.8%. Compare that to encapsulation efficiency observed for the using the method of the instant application as discussed on pages 19 and 20 of the instant application as Example 2. Applicant prepared microspheres of the water-insoluble salt of pyroGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2 complexed with carboxylated p(dl-LGA) which had an initial peptide content of 9.8% as determined by nitrogen analysis. The complex was dissolved in DCM which was slowly added to a PVA solution which resulted in the formation of microspheres having a peptide content of 8.4%. The encapsulation efficiency for the microspheres prepared according to Example 2(b), therefore, is calculated to be

85.7% (8.4 ÷ 9.8 × 100 = 85.7%). It is well-established principle that extrinsic evidence, such as unexpected results, bolsters the non-obvious nature of the claimed invention. *Graham v. John Deere Co.*, 38 U.S. 1, 148 U.S.P.Q. (BNA) 459 (1966).

Notwithstanding the improved encapsulation efficiency of the claimed process over Herrmann, the instant process is not legally obvious based on the primary reference. Herrmann differs from the instant method in two significant instances. Herrmann requires the use of two solvents, i.e., methanol/ethanol used as the solvent of the peptide and CH_2Cl_2 as the solvent for the polymer. Herrmann also does not recognize the inherent benefits of first forming a complex of the peptide with an anionically or cationically functionalized polyester. As discussed previously, it is this discovery that resulted in greater encapsulation efficiency. As argued previously, neither Shalaby nor Fong provide the requisite motivation to combine their teachings with those of Herrmann. The Examiner has not established a prima facie case of obviousness based on the teachings of Herrmann in combination with Shalaby and Fong by failing to specifically identifying the suggestion to combine in any of the cited references. Since the onus is on the Examiner to do so, and since the Examiner has not, the rejection of claims 17-22, 25, 28 and 29 under 35 U.S.C.

§103(a) as obvious over Herrmann in view of Shalaby and Fong must be rescinded[5].

3. Claims 17-22, 25, 28 and 29 stand rejected under 35 U.S.C. §112, first paragraph, for not enabling the preparation of microcapsules comprising peptides other than LHRH. Applicants respectfully disagree. When rejecting a claim under the enablement requirement of section 112, the examiner bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts. *See* MPEP §2164.04. The Examiner states that with respect to the making of microspheres containing somatostatin, that "there is no evidence that they could be prepared by the same method." The Examiner clearly misinterprets the law by placing the burden incorrectly on the Applicant.

[5] The Examiner's comments regarding the order of mixing of components is not understood since there is no mixing of components as alleged by the Examiner. The 1st step of the method of claim 17 requires the dissolving of a salt of a peptide complexed with an anionically or cationically functionalized biodegradable polyester. Applicant requests clarification of the Examiner's reasoning.

Applicant provided sufficient guidance to enable the process as described in claims 17-22, 25, 28 and 29. As recognized by the Examiner, a working example for making microcapsules according to claims 17-22, 25, 28 and 29 containing LHRH is discussed in the present application. This is legally sufficient[6].

> The lack of working examples is one consideration in the overall analysis of lack of enablement. *In re Colianni*, 561 F.2d at 224, 195 USPQ at 153. MPEP §2164.02 states "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." When considering the factors relating to a determination of non-enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled. In other words, lack of working examples or lack or evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. The presence of only one working example should never be the sole reason for making a scope rejection. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.
>
> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose

---

[6] Based on the reasoning provided by the Examiner, the rejection of claims 17-22 and 30 under 35 U.S.C. §112, first paragraph, was clearly erroneous.

> other methods by which the claimed invention may be made does not render a claim invalid under Section 112. *Spectra-Physics, Inc. v. Coherent, Inc.* 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987). Accordingly, the case law makes clear that properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Examiner's reliance on Herrmann to support his position that the instant application is not enabling is unpersuasive. As noted by Herrmann, "the suitability of a particular technique is mainly determined by the solubility of the peptide and the drug which are usually fixed…Depending on the solubility properties of the drug it can be either dissolved or dispersed." Applicant does not disagree with this statement. As previously argued, the Applicant recognized the inherent problems associated with peptide solubility. As stated on page 1, lines 33-34 of the instant application, the Applicant stated that "[t]he main hurdle to achieving higher encapsulation efficiency of the peptides is their water solubility." The Applicant discovered the aqueous solubility of the drug, "without sacrificing its potency, is simply forming reversible water insoluble salts…found to exhibit good solubility in organic solvents such as dichloromethane (DCM)." The Applicant's statements in his response to the Office Action dated July 30, 2003, as noted by the Examiner, i.e., that the limiting step is obtaining a solution, not a suspension, are consistent. Orsolini et

al. did not recognize the inherent benefits of forming reversible water insoluble salts which resulted in the less-desirable formation of a suspension and not a solution which resulted in poor encapsulation efficiency[7].

The Examiner fails to provide reasonable extrinsic evidence casting doubt on feasibility to employ the method of claims 17-22, 28 and 29 to produce microspheres comprising an anionically or cationically functionalized biodegradable polyester and one of the biologically active peptides found in claim 25. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The burden placed on the examiner is reflected in MPEP §706.03. Claims 17-22, 28 and 29 are, therefore, legally enabled under 35 U.S.C. §112, first paragraph. Applicant respectfully requests reconsideration of the rejection of same and withdrawal of said rejection.

[7] Applicant does not understand the relevance of the Examiner's statement that Shalaby teaches that complexes of peptides with a charged polyester ***should*** be dissolved in acetone rather than dichloromethane and requests clarification thereof.

Request for Rejoinder

Applicant submits that claim 17 is a generic claim and based on the above arguments is in a condition for allowance. Upon the allowance of a generic claim, an Applicant is entitled to consideration of claims to additional species which are written in dependent form as provided for by 37 C.F.R. §1.141. Applicant respectfully requests that withdrawal of claims 23, 24, 26 and 27 be rescinded and that said claims be reconsidered.

In summary, it is believed that the instant application is now in an allowable condition and such allowance is earnestly solicited.

Examiner Borin is invited to telephone the Applicant's representative at the telephone number indicated below to facilitate the prosecution of this application. The Commissioner is hereby authorized to charge any additional fees deemed necessary to Deposit Account 50-0590.

Respectfully submitted,

Date: 11-19-2004

Alan F. Feeney
Attorney for Applicant(s)
Reg. No. 43,609

Biomeasure, Incorporated
27 Maple Street
Milford, MA 01757-3650
(508) 478-0144 (Telephone)
(508) 473-3531 (Facsimile)